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FINAL TECHNICAL REPORT

ONR CONTRACT #N00014-87-K-0518

Analysis of neural systems involved
in modulation of memory storage

06/01/87 - 05/31/90

James L. McGaugh, Principal Investigator

The research supported by this contract over the past three years examined the role of neuromodulatory systems in the modulation of memory storage processes. The research was based on extensive evidence from previous studies indicating that memory storage processes are modulated by neuromodulatory systems activated by learning experiences. It is well documented that, in laboratory animals, retention is modified by posttraining administration of stress-related hormones as well as neurotransmitters and drugs that influence hormonal and neurotransmitter systems (McGaugh, 1989; McGaugh and Gold, 1989). Research in ~~the~~ laboratory has examined the effects of treatments affecting adrenergic, cholinergic, opioid peptidergic and, most recently, GABAergic systems (Brioni and McGaugh, 1988; Castellano, Brioni and McGaugh, in press). Previous studies indicated that these neuromodulatory systems may influence memory through effects involving the amygdaloid complex. More generally, the findings of preliminary studies suggested that the amygdala may serve to integrate the effects of neuromodulatory systems on memory storage (McGaugh, 1989).

The aim of the research supported by this contract was, 1) to increase our understanding of the locus of brain regions involved in the effects, on memory of treatments affecting neuromodulatory systems, and 2) to determine whether treatments affecting memory storage work through a common set of brain systems.

Experiments supported by this contract have provided additional evidence that treatments affecting hormonal and neurotransmitter systems influence memory through effects involving the amygdala. We have found that, in rats, retention, as assessed in two tasks (inhibitory avoidance and Y-maze discrimination) is enhanced by posttraining intra-amygdala injections of the opiate antagonist naloxone (Introini-Collison, Nagahara and McGaugh, 1989). The further finding that this effect is blocked by concurrent administration of the β -adrenergic antagonist propranolol is consistent with previous findings indicating that the effects involve activation of β -adrenergic receptors within the amygdaloid complex. Presumably, such effects are due to blocking of the inhibitory influence of opioid peptides on the release of norepinephrine (NE). We have also found that the effects of posttraining intra-amygdala injections of NE on memory are blocked by lesions of the stria terminalis (ST) (Liang, McGaugh and Yao, 1990). These findings provide further evidence that amygdala efferents mediated by the ST are critical for the memory-modulating effects of treatments affecting amygdala functioning.

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We have also completed an extensive set of experiments examining the effects of GABAergic drugs on memory. We confirmed and extended previous findings indicating that, when administered systemically posttraining, retention is enhanced by GABAergic antagonists, including picrotoxin and bicuculline, and impaired by GABAergic agonists, including the GABA-A agonist muscimol and the GABA-B agonist baclofen (Brioni and McGaugh, 1988; Castellano, Introini-Collison, Pavone and McGaugh, 1989; Castellano, Brioni, Nagahara and McGaugh, 1989; Castellano and McGaugh, 1989; Castellano, Brioni and McGaugh, in press; McGaugh, Castellano and Brioni, 1990). Comparable effects are found in several aversively-motivated tasks. Further the effects are not due to the induction of state-dependency (Castellano and McGaugh, 1989; Castellano and McGaugh, in press). More importantly, we have found that effects comparable to those produced by systemic injections of GABAergic drugs are produced when these drugs are administered via intra-amygdala injections (Brioni, Nagahara and McGaugh, 1989; Castellano, Brioni, Nagahara and McGaugh, 1989). The memory modulating effects of GABAergic antagonists, like those we produced by NE and naloxone, are blocked by propranolol (unpublished findings). We have also found (unpublished findings) that the effects of GABAergic drugs on memory are blocked by lesions of the amygdala and dorsal hippocampus, but are not blocked by lesions of the caudate. Thus, these findings provide additional evidence indicating that a variety of hormonal and neuromodulatory systems affect memory through influences involving the amygdaloid complex. In addition, recent findings of the effects of hippocampal lesions suggest that that structure, as well may be involved in mediating the effects of neuromodulatory systems on memory storage. As has been reported in many previous studies, lesions of the amygdala, hippocampus and caudate impair performance in the inhibitory avoidance task (unpublished findings; Cahill and McGaugh, in press).

In other recent work we have found that the memory-modulating effects of oxotremorine and scopolamine (a cholinergic agonist and antagonist, respectively) are blocked by lesions of the ST (Introini-Collison, Arai and McGaugh, 1989). These effects are highly comparable to those obtained in previous studies of the effects of ST lesions on the memory-modulating effects of naloxone, β -endorphin, and epinephrine (McGaugh, 1990). We have also found that, in contrast to these other findings, that retention is not influenced by posttraining intra-amygdala injections of cholinergic drugs. Memory is, however, influenced by injections administered prior to training. Thus, the cholinergic effects appear to involve different mechanisms.

We have also obtained evidence indicating that different brain regions may be involved in regulating learning of different types of tasks. For example, spatial learning in a Morris water maze is impaired by pre-training (but not posttraining) intra-septal injections of muscimol (Brioni, Decker, Gamboa, Izquierdo and McGaugh, in press). These effects appear to be mediated by GABAergic regulation of the septo-hippocampal cholinergic system, such effects influence high affinity choline uptake in the hippocampus.

These are the major findings of research supported by this contract during the past several years. These findings, as well as the findings of a number of related experiments are summarized in detail in the accompanying papers. The findings have provided significant information related to the two major aims of the proposal, as summarized above. In particular, these findings

provide strong support for the finding that the amygdala serves to orchestrate the interaction of hormonal and neurotransmitter systems in regulating memory storage. And, such findings indicate that an account of the neurobiology of learning and memory must include an understanding of the roles of neuromodulatory systems in regulating the cellular neurobiological process underlying learning and memory.

STATEMENT "A" per Joel Davis
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